5 The Value of Adrenal Imaging in Adrenal Surgery

Bruno Niederle, Gertraud Heinz-Peer, Klaus Kaczirek, Amir Kurtaran

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5.1 Introduction

Clinically inapparent adrenal masses (incidentaloma, adrenaloma) are discovered inadvertently during abdominal imaging for several clinical conditions not related to adrenal disease. By definition, the term incidentaloma excludes patients undergoing localization for suspected hormonal excess or those undergoing a staging work-up for previously diagnosed cancer [26].

When detected, these adrenal tumors raise challenging questions for physicians and patients. Not all incidentalomas are of clinical importance and therefore candidates for treatment. After a careful clinical, biochemical and radiological evaluation patients need to be selected for surgery. The indication for surgical treatment and the type of surgical approach depend on hormonal activity, tumor size, localization and suspected malignancy.

Independent of their size, functioning or subclinically autonomous adrenal tumors are candidates for surgery, while non-functioning tumors are not (Fig. 1). According to the literature the indication for the surgical treatment of non-functioning adrenal lesions depends on their size and indirect signs of malignancy. *Non-functioning tumors smaller than 30 mm* are usually followed up. In instances of radiologically documented growth they become candidates for operation. *Non-functioning tumors between 30 and 50 mm* present a relative indication for surgery, since malignancy rarely occurs. The patient's age, co-morbidities and the patient's concern influence therapy. *Non-functioning tumors larger than 50 mm* need a total histological work-up since malignancy increases dramatically with size.

5.2 Fine-Needle Aspiration

The poor prognosis of adrenocortical carcinoma (ACC) makes early diagnosis very important. A reliable histopathological diagnosis from adrenal biopsy, by *fine-needle aspiration (FNA)* or *adrenal core biopsy,* would be desirable but is controversial because of its questionable accuracy and its risks. Whereas sensitivity is high with adrenal metastases (particularly lung, breast and kidney), its accuracy is questionable in the context of primary adrenal tumors (adenomas versus ACC). An overall sensitivity for malignancy of 94.6% and specificity of 95.3% was documented in a recently published ex vivo adrenal core biopsy study [67], when sufficient biopsy specimens were obtained. Comparing the sensitivity and specificity in detection of malignancy of ^{75}Se-selenonocholesterol scintigraphy (^{75}Se-NCS; for further details see below), computed tomography (CT), magnetic resonance im-

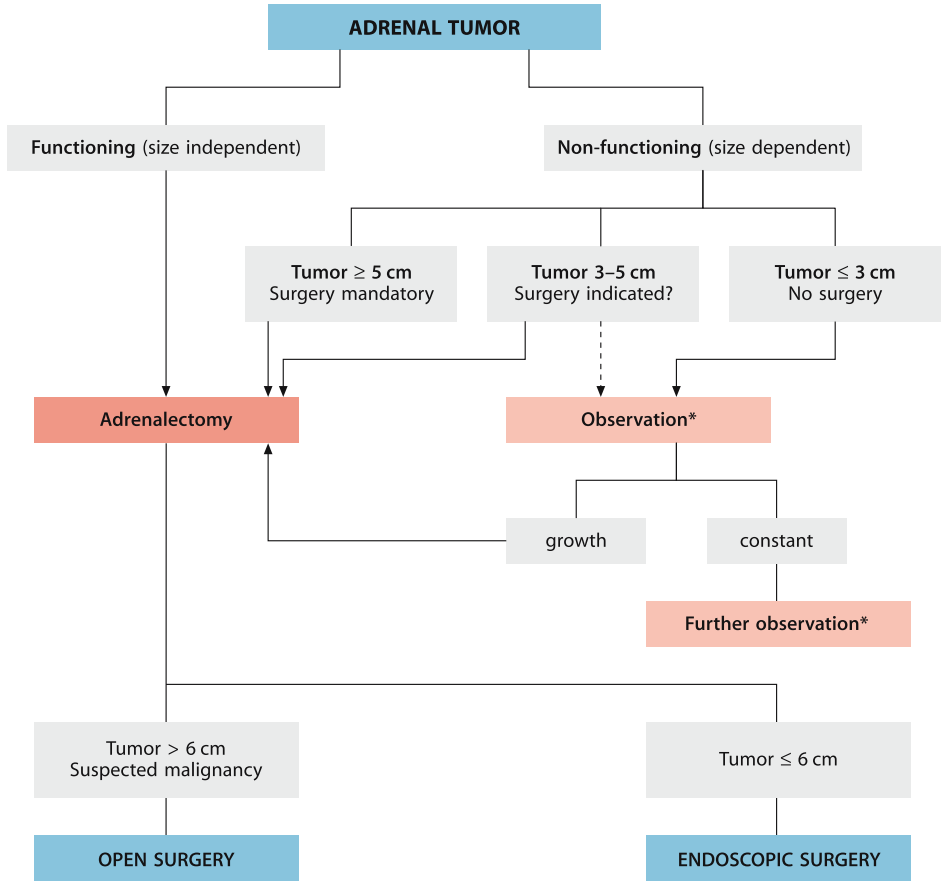


Fig. 1. Treatment algorithm of adrenal tumors depending on hormone function and size (*followed by CT or MRI every 6 months for 2 years)

aging (MRI) and FNA, ^{75}Se-NCS and FNA were more sensitive than CT and MRI [13, 46]. However, in clinical practice it remains to be shown whether the benefits of FNA outweigh the risks of the procedure. Pheochromocytoma must always be excluded before FNA of any adrenal mass is attempted in order to avoid the risk of a life-threatening hypertensive crisis. A benign FNA cytological diagnosis does not exclude malignancy because of the high rate of false-negative rates. FNA has well-documented side effects such as hemorrhage, pneumothorax or needle track seeding.

The development of semiquantitative adrenal imaging techniques (CT, MRI) has reduced the necessity for cytological differentiation of adrenal lesions [9]. They may help to differentiate between benign and malignant adrenal lesions. Therefore their results strongly influence further treatment (observation or

Table 1. Endoscopic adrenalectomy: indications and contraindications

Indication Functioning/ non-functioning tumors	Relative indication Functioning/ non-functioning tumors	Contraindication Adrenocortical cancer
≤6 cm	≥6 cm Metastasis Very obese patients Major upper abdominal surgery in history	Suspected malignancy

extirpation) and the surgical strategy (open or endoscopic) in patients selected for surgery.

Endoscopic adrenalectomy represents the "New Golden Standard" in the surgical treatment of benign adrenal lesions up to 60 mm [51, 62]. Open adrenalectomy is recommended for patients with suspected malignant disease and for tumors larger than 60 mm (Fig. 1, Table 1). Whether endoscopic adrenalectomy should be proposed for larger (>60 mm) or potentially malignant tumors remains controversial [12, 15, 29].

5.3 Angiography

Angiography has lost its former importance [16] in classifying adrenal tumors and assessing their relationship to adjacent tissue. Angiography of an unknown pheochromocytoma can cause life-threatening hypertensive crisis [16]. Several morphological (ultrasonography, computed tomography, magnetic resonance imaging) and functional imaging studies (selective hormonal venous sampling, scintigraphic techniques) may be applied. In specific clinical situations a combination of morphological and functional adrenal imaging studies is mandatory to answer the following important questions which influence the therapeutic strategy.

5.4 Questions Regarding Adrenal Imaging

1. What is the size of the tumor?
2. Is the lesion solitary or multiple in the affected adrenal gland?
3. Is the contralateral adrenal gland normal or affected?
4. Are there indirect signs of malignancy (prediction of the status by taking into account the appearance of the lesion (homogeneous? inhomogeneous? necrotic areas? fat content? enhancement of the contrast medium?)?
5. Are there direct signs of malignancy (rapid growth in follow-up examinations? infiltration of adjacent organs/structures? tumor-thrombus in the inferior vena cava or the renal vein?)?

5.5 Tumor Size and Malignancy

The size of the adrenal mass, best documented by CT or MRI, is a good but not the best indicator for the prediction of the histological status of an adrenal lesion. The prevalence of ACC is clearly related to the size of the tumor: ACC are usually large (>50 mm in diameter) and adrenal adenomas are usually small (≤50 mm); nevertheless relatively small adrenal cancers and large benign tumors occur with measurable frequency [2]. ACC accounts for 2% of tumors ≤40 mm, 6% of tumors from 41 to 60 mm, and 25% of lesions greater than 60 mm [26]. As shown recently, according to their biochemical profile, 144 (91%) of 158 adrenal lesions were classified as benign and 14 (9%) malignant [62]; 124 (78%) lesions were smaller than 60 mm, 34 (22%) larger than 60 mm, respectively; 25 (17%) of 144 benign lesions were larger than 60 mm; 5 (36%) of 14 malignant tumors were less than 60 mm (i.e. 4% of all lesions smaller than 60 mm); 9 (64%) of 14 malignant lesions were larger than 60 mm and 9 (26%) of 34 tumors larger than 60 mm were classified as malignant. On histopathological examination 74% of all tumors larger than 60 mm were classified as benign. Therefore, the initial size of a lesion *alone* cannot predict the biological behavior of an adrenal lesion and cannot influence the selection of the surgical strategy. Endocrine surgeons and endocrinologists must also take into account that CT and MRI at times underestimate the true size of adrenal tumors [37, 38, 41, 42]; thus the size has to be interpreted with caution [38].

Considering size alone when choosing the surgical access would lead to an endoscopic removal of up to 36% of adrenal malignant tumors [2, 10, 62], which might lead to a high recurrence rate. Therefore additional imaging criteria are mandatory [2].

5.6 Radiological Imaging

5.6.1 Ultrasonography

Ultrasonography (US) is inexpensive, detects adrenal lesions and discriminates cystic from solid lesions. However, ultrasound has a low sensitivity for detection of small masses compared to other modalities (see below). US poorly characterizes solid adrenal masses and poorly detects extension into adjacent structures or is, in the majority of situations, unable to exclude distant metastases. Therefore US seems of no value in answering the questions raised above, for follow-up, for selection of patients who need further treatment, or for planning any surgical procedure.

5.6.2 Computed Tomography

Computed tomography (CT) is generally the preferred primary modality for evaluation of the adrenal glands. CT is fast, readily available, and offers the highest spatial resolution. Helical scanning, using 3–5 mm thick slices to reduce volume averaging, improves the accuracy of density measurement of small adrenal lesions. The latest generation of CT machines (multidetector CT) allows rapid acquisition of very thin slices with excellent spatial resolution. An isotropic data set provides the basis for performance of multiplanar reconstructions and thereby viewing adrenal masses in multiple planes. In addition, anatomic details and relation of adrenal lesions to adjacent structures can be better evaluated. This proves to be extremely helpful in the current era of laparoscopic adrenalectomy.

Contrast CT and delayed images help to characterize enhancement of vessels in the region of the adrenal. Unenhanced CT, however, is often the key series in the evaluation of "incidentalomas" or potential adenomas (Figs. 2, 3). Diagnosis of adenoma when the density is <10 Hounsfield Units (HU) has a sensitivity of 74% and a specificity of 96% [35]. Since many adrenal lesions are incidentally detected on contrasted CT, enhancement patterns of adrenal lesions have been studied to help obviate the need for a separate non-contrast CT, which would require imaging at a separate visit. Immediate post-contrast density is variable and non-discriminatory. Several authors have reported high sensitivity and specificity for density readings on delayed post-contrast CT, but varying cut-off values (25–37 HU) and delay times have been used (15–60 min). In one study of 78 lesions, all adenomas had CT <37 HU and all non-adenomas had a density >41 HU with a 30 min delay after contrast [75]. This yielded both a specificity and sensitivity for adenoma of 100%, respectively. Another recent study showed that no malignant lesions had densities of less than 25 HU at a 15 min delay [43]. This allows 100% specificity with only minimal interruption of the patient flow in CT. The same study showed 96% sensitivity and 100% specificity for adenoma using a 40% washout after a 15 min delay compared to immediate post-contrast images [36].

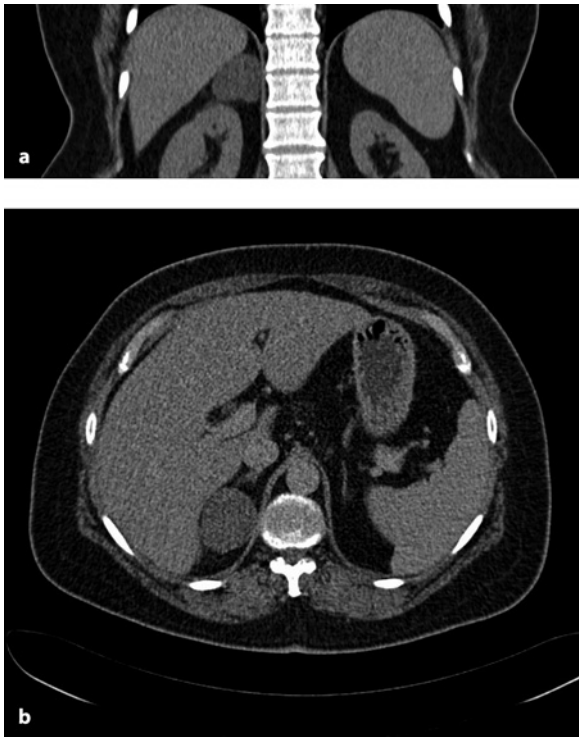


Fig. 2a, b. Benign adrenal adenoma in CT. Twenty-seven-year-old asymptomatic female patient: incidentally detected 40 mm non-functioning adrenal mass in the right adrenal gland. Density of the lesion was 4 HU on unenhanced coronal reconstructed CT scan (**a**) and 39 HU on delayed enhanced CT scan (**b**) with a percentage wash-out of >50% – typical characteristics of a benign adenoma

5.6.3 Magnetic Resonance Imaging

With the advent of dynamic gadolinium enhanced and chemical shift (CSI) techniques, magnetic resonance imaging (MRI) has become a well-accepted diagnostic method for the characterization of adrenal masses. Many studies have shown sensitivities and specificities for differentiation of adenomas from non-adenomas ranging between 81–100%, respectively [27, 34, 39, 40, 52, 69].

Korobkin et al. [35] and Outwater et al. [58] showed that the presence of lipid in many of the examined adenomas accounted for the low attenuation on unenhanced CT, causing a loss in signal intensity on chemical shift MR imaging.

In addition, MRI has the best contrast resolution for adrenal evaluation. The spatial resolution is adequate for detection of lesions as small as 0.5–1.0 cm. MRI adrenal studies should include T1-weighted axial images for anatomic detail and T2-weighted axial images [57]. Fat suppression is used so that heavily T2-weighted images are not degraded by chemical shift artifact from the fat which surrounds the adrenals. Contrast helps to characterize enhancement patterns, and on delayed post-contrast MRI series washout

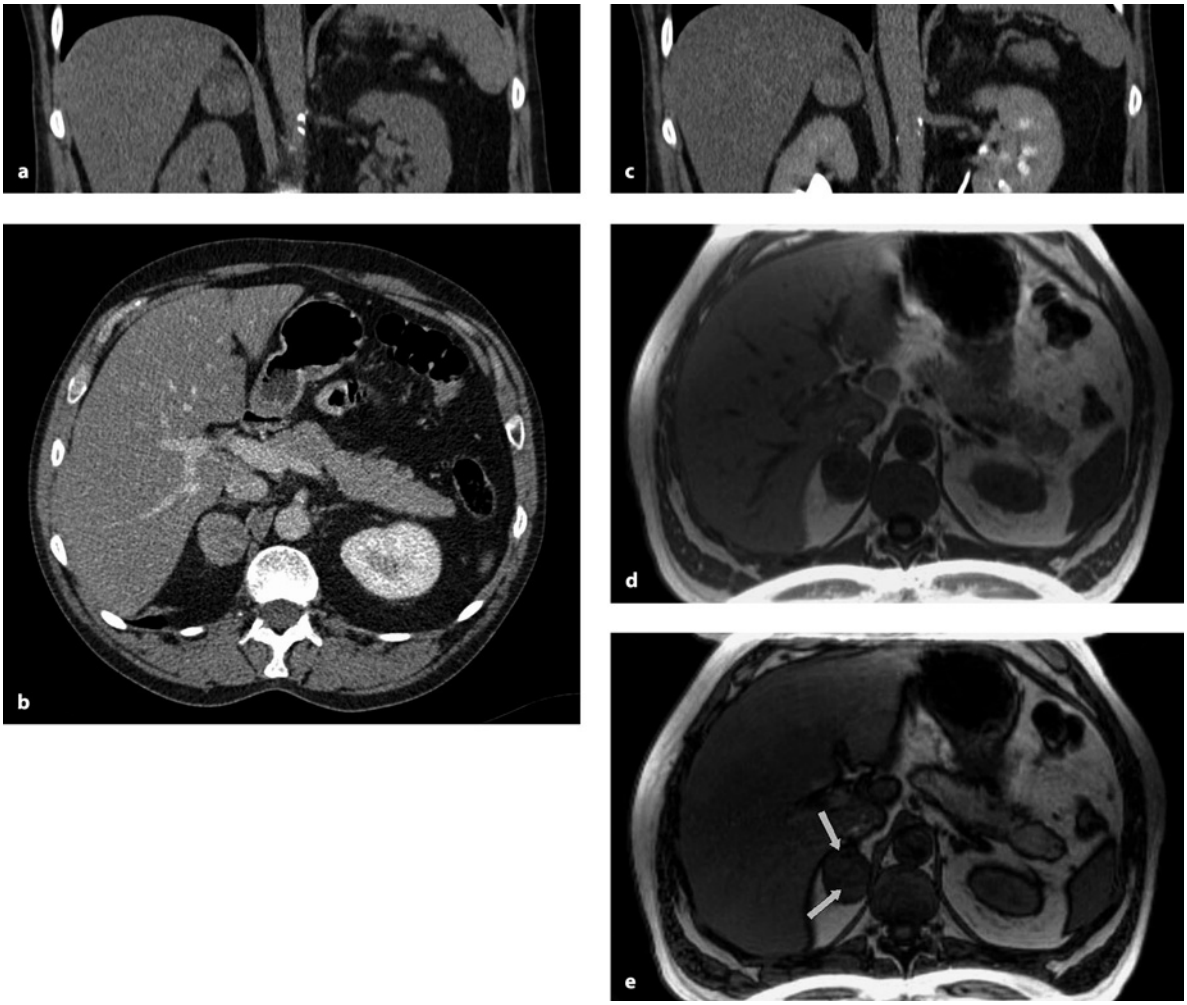


Fig. 3a–e. Benign adrenal adenoma in CT and MRI. Fifty-six-year-old male patient with lung cancer: staging examinations documented a non-functioning, 45 mm mass in the right adrenal gland. Density of the lesion was 6 HU on unenhanced coronal reconstructed CT scan (**a**). On contrast-enhanced scans (**b**) the lesion showed minor enhancement (55–88 HU) and rapid wash-out on delayed scans (**c**), indicating a benign lesion. On MRI (**d**, **e**) some spotty areas (*arrows*) of significantly decreased SI were demonstrated on opposed-phase images (**e**) again indicative of a benign lesion

curves similar to that on delayed post-contrast CT can be achieved.

By definition [52], an adrenocortical adenoma appears hypo- or isointense relative to the liver on T1-weighted images and hyper- or isointense to the liver on T2-weighted images, and has lost signal intensity on opposed-phase images compared with in-phase images (Fig. 3). In addition, a quick washout on gadolinium-enhanced studies is considered more typical of benign than of malignant lesions [39].

Lesions with marked enhancement on delayed gadolinium series are considered more likely to be malignant (Fig. 4). The diagnosis of carcinomas and metastases (Fig. 5) is based on findings from chemical shift and gadolinium enhanced studies rather than on the signal intensities of conventional techniques [52].

High signal intensity of homogeneous adrenal masses on T2-weighted images and no signal loss on opposed-phase images compared with in-phase images is considered to indicate a pheochromocytoma (Fig. 6) [27, 30]. In addition, an atypical pheochromocytoma may be of medium signal intensity on T2-weighted images or may appear inhomogeneous, especially when they are cystic pheochromocytomas [30].

Lesions appearing heterogeneous on T1 and heterogeneous on T2 and showing a peripheral nodular enhancement and central hypoperfusion on contrasted MRI were characterized as adrenal carcinoma. The

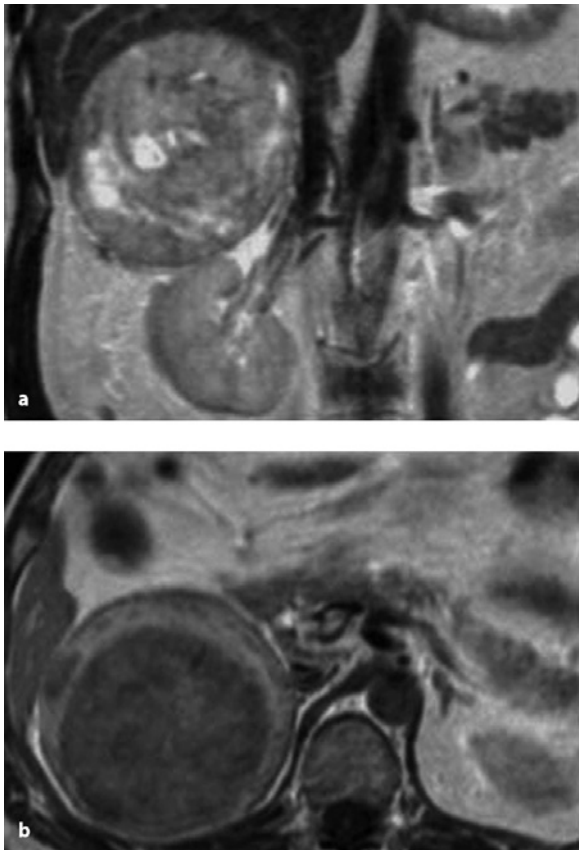


Fig. 4a, b. Adrenocortical cancer in MRI. Sixty-one-year-old male patient with an incidentally 8 cm mass in the right adrenal gland. T2-weighted images showed a sharply demarcated inhomogeneous mass (**a**). There was no evidence of a fat containing lesion and on contrast-enhanced images the mass showed a predominantly peripheral enhancement with central necrosis (**b**)

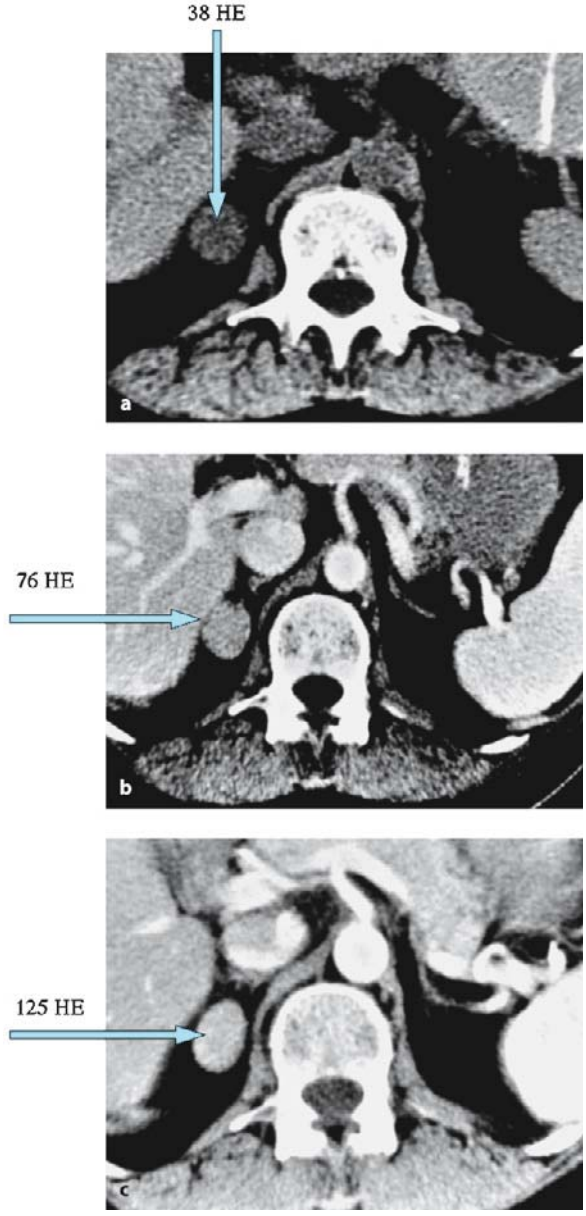


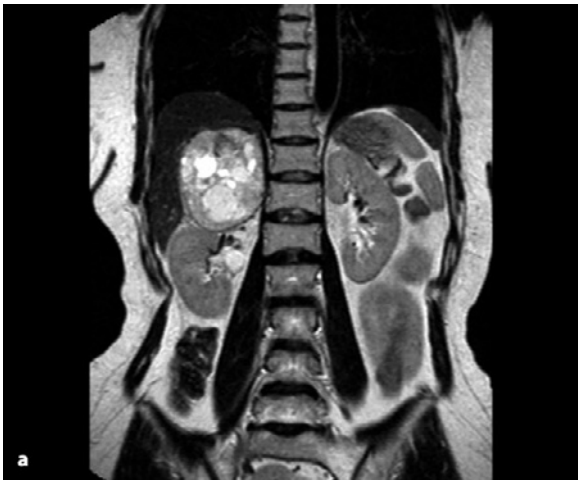
Fig. 5a–c. Adrenal metastasis. Sixty-five-year-old female patient with breast cancer: abdominal CT scan revealed a 20 mm mass in the right adrenal gland with a density of 38 HU on unenhanced scans (**a**), an increasing enhancement on the arterial phase (**b**) and the 3 min delayed series (**c**), indicating a malignant lesion (metastasis)

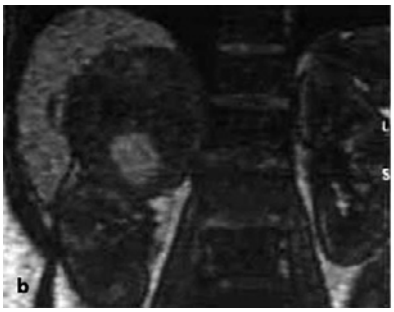
invasion of adjacent organs or the inferior vena cava was also considered typical of adrenal carcinoma [30].

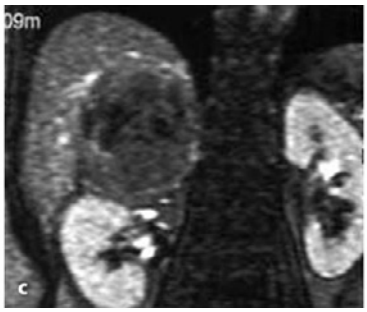
The presence of fat-containing areas that showed signal intensity equal to those of subcutaneous and retroperitoneal fat at all pulse sequences was the criterion for myelolipoma. The suppression of fat-containing areas on fat-saturation MRI was also considered typical of myelolipoma. [30]. The signal intensity of cysts may depend on their content [30]; however, round adrenal masses with sharp margins in which there was no gadolinium enhancement were diagnosed as adrenal cysts.

In recently published series including a total of 229 adrenal masses in 204 patients, the sensitivity of MRI for the differentiation of benign and malignant adrenal masses was 89%, the specificity 99%, and the accuracy 93.9%. This resulted in a positive predictive value (PPV) of 90.9% and in a negative predictive value (NPV) of 94.2% [27, 30].

To transfer this experience into daily surgical practice a prospective protocol was conducted to prove the suitability of gadolinium-enhanced MRI with chemical shift studies (CSI) for predicting the status of adre-







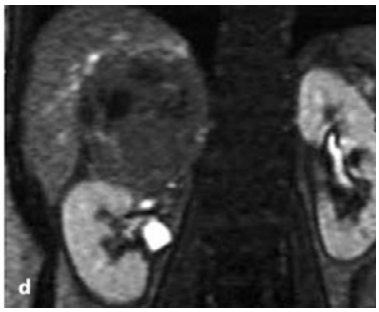


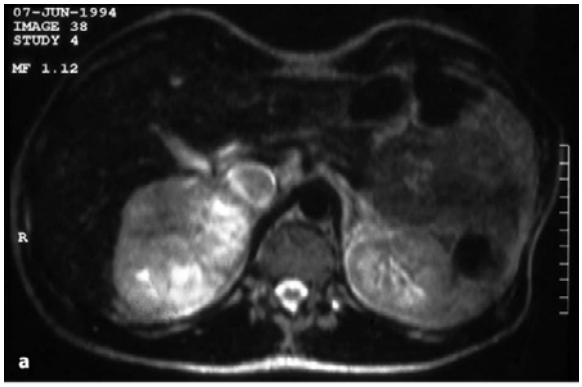
Fig. 6a–d. Benign pheochromocytoma in MRI. Forty-two-year-old female patient with severe hypertension MRI showed a 9 cm predominantly solid mass in the right adrenal gland with some cystic areas on T2-weighted sequence (**a**) and with a hypertense structure on T1-weighted sequence, indicating a hematoma (**b**). After i.v. Gd-DTPA, the mass shows only a mild inhomogeneous enhancement (**c**) and rapid wash-out (**d**)

nal tumors irrespective of the tumor size [61] and for planning the surgical procedure [62].

As summarized in Table 2, gadolinium enhanced MRI with CSI diagnosed 120 of 137 tumors (88%) as benign, and 5 (3%) and 12 (9%) of 137 tumors as borderline (epithelial tumors with high malignant potential) and malignant, respectively. During staging examinations no distant metastases, or invasion into adjacent organs or vessels were diagnosed. Histopathological examinations classified 120 (88%) of 137 adrenal tumors as benign, 3 (2%) as borderline and 14 (10%) as malignant. MRI correctly predicted the dignity (benign, borderline and malignant) in 130 of 137 adrenal lesions (sensitivity: 95%). By MRI two

Table 2. Results of MRI ["gadolinium enhanced" MRI with "chemical shift imaging (CSI)"] and histopathology in a prospective study

Predicted status by MRI	*n* (%)	Histopathology of the adrenal tumor (size)
Benign	120 (87.6)	117 benign [98%] 2 ACC (25 mm; 50 mm) 1 malignant pheochromocytoma (90 mm)
Borderline	5 (3.6)	3 benign 2 borderline classification unclear
Malignant	12 (8.8)	1 borderline 7 ACC 3 metastasis 1 malignant pheochromocytoma
Total	137 (100)	120 benign [88%] 3 borderline [2%] 14 malignant [10%]



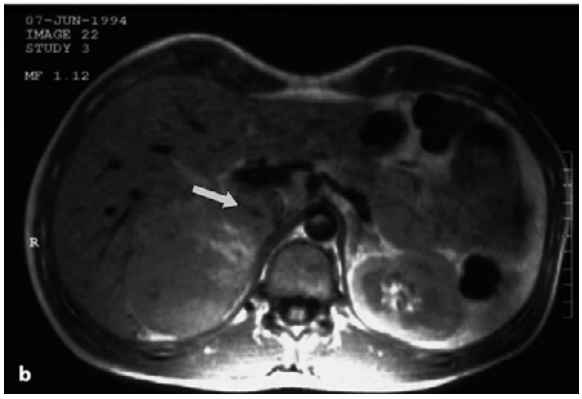


Fig. 7a, b. Malignant pheochromocytoma with tumor thrombus. Fifty-year-old male patient with right flank pain. MRI revealed a 9 cm mass in the right adrenal gland appearing very inhomogeneous on T2-weighted images (**a**) and showing an infiltration of the VCI after Gd–DTPA administration (**b**), indicating a malignant tumor

cortisol producing ACC (25 mm; 50 mm) and one malignant pheochromocytoma (90 mm) were misdiagnosed as benign tumors. Both patients with the ACC underwent an uneventful transperitoneal laparoscopic adrenalectomy. The patient with the malignant pheochromocytoma was operated on using an open approach. All three patients are free of disease at 12, 38 and 48 months, respectively. One further tumor (80 mm) diagnosed as benign on MRI had a borderline tumor on histopathological examination and was removed by open adrenalectomy. Three tumors (55 mm; 65 mm; 90 mm) were diagnosed as borderline on MRI. Histopathology revealed adenomas with degeneration. With improving endoscopic experience nine patients with adrenal masses (five pheochromocytomas, three non-functioning adenomas, one schwannoma) larger than 6 cm and benign characteristics on MRI were operated on laparoscopically. All of these patients had an uneventful postoperative course and histopathological examination proved benign disease in all patients [61].

In addition multiplanar imaging helps to detect extension of the adrenal tumor into adjacent organs and vessels (Fig. 7). These findings are very important because they definitively document malignancy. If surgery is indicated, an open approach has to be performed. MRI proves to be an adequate alternative for imaging of adrenals without radiation exposure. MRI is the first choice in patients with an allergy to iodine contrast media and in patients with renal insufficiency.

5.6.4 The Value of a Combined Use of CT and MRI in Characterizing an Adrenal Mass

To differentiate a benign adenoma from ACC or from a metastasis non-enhanced CT should be performed after appropriate biochemical testing and the attenuation of the mass should be quantified (Fig. 8). If the attenuation of the adrenal mass is 10 HU or less, the mass is an adenoma and the work-up can be stopped. If the attenuation is over 10 HU, contrast-enhanced CT should be performed and washout calculated. A washout of over 50% on a 10-min delayed CT implies an adenoma. If the mass remains indeterminate, MRI should be performed. The characteristics of benign and malignant adrenal lesions in dynamic gadolinium enhanced MRI with CSI are summarized in Table 3. Adrenal lesions suspected to be malignant have to be operated on. Adrenal biopsy could be helpful in the oncologic patient to document metastatic disease, indicating an advanced disease that is sometimes not amenable to surgical resection and potential cure.

5.6.5 Adrenal Venous Sampling

In 15–25% of patients hypercortisolism is ACTH independent (Cushing's syndrome). In the majority the cause is a primary adrenal neoplasm, usually a benign adenoma rarely a carcinoma, greater than 20 mm in diameter. In a small group of patients bilateral micro- or macronodular hyperplasia is present.

Once the diagnosis of primary aldosteronism (Conn's syndrome) is confirmed the different therapeutic strategies make it important to separate patients with unilateral adrenal tumors (60–80%) from those with unilateral and bilateral adrenal hyperplasia (idiopathic aldosteronism). Primary aldo-

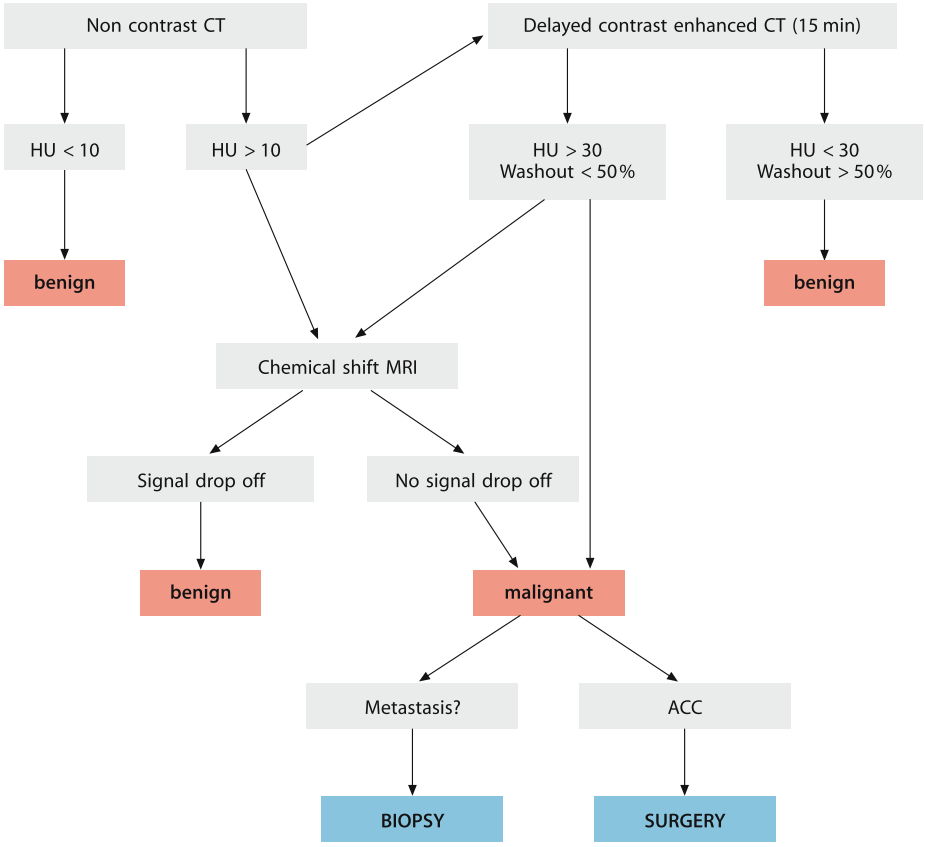


Fig. 8. Work-up algorithm to differentiate benign and malignant adrenal tumors (*HU*, Hounsfield units; *CT*, computed tomography; *MRI*, magnetic resonance imaging)

Table 3. Characteristics of benign and malignant adrenal lesions in dynamic gadolinium enhanced MRI with CSI (*SI*, signal intensity)

	Malignant lesion	Benign lesion
Enhancement of gadolinium	Strong	Moderate
Wash-out phenomenon	Moderate	Quick
CSI: decrease of SI on opposed phase images	Weak	Strong

steronism has uncommonly been associated with ACC [44].

Appropriate treatment depends on a correct morphological diagnosis. Therefore it is necessary to employ radiological and/or scintigraphic localization techniques. The final diagnosis of bilateral hyperplasia in Cushing's syndrome and in Conn's syndrome depends on the determination of cortisol or aldosterone in adrenal venous sampling [11]. In Conn's syndrome this is not only the oldest but also the most precise localization technique available [47, 82], because the solitary lesions causing aldosteronism are smaller than 10 mm in the majority of patients. Magilli [47] and Rossi [66] demonstrated that neither adrenal CT nor MRI is a reliable method to differentiate primary aldosteronism from other adrenal tumors. Adrenal vein sampling seems essential to establish the correct diagnosis of primary aldosteronism [78].

5.7 Nuclear Medicine Imaging

Radiological imaging modalities such as CT and MRI give excellent anatomic details due to their high image

resolution, which is very important in planning the operation [5] but provides no information on the function of an adrenal mass.

Both adrenomedullary and adrenocortical scintigraphy of adrenal glands using specific radiopharmaceuticals have the advantage of providing functional metabolic information for lesion characterization [24, 50].

Scintigraphic imaging may help to discriminate between benign and malignant lesions [1]. In patients with bilateral adrenal masses scintigraphy is able to differentiate between unilateral cortical/medullary tumors and bilateral hyperplasia [24, 25]. Finally, when a malignancy is present, scintigraphic techniques have the advantage of providing unique information concerning the entire body with only one administration of tracer without an additional radiation dose to the patient [59].

Based on their different natures, radiological as well as scintigraphic techniques should be considered complementary and both are necessary in the investigation of the patients [24, 59].

5.7.1 Adrenocortical Scintigraphy with ^{131}I-6β-iodomethyl-norcholesterol (NP-59), ^{131}I-19-iodocholesterol or ^{75}Se-selenocholesterol

Adrenocortical scintigraphy with NP-59 provides functional characterization of the adrenal glands due to the uptake of the radiotracer by functioning adrenal cortical tissue (Fig. 9). After intravenous injection this tracer is bound to low-density lipoproteins, which are transported by the circulation to specific low-density lipoprotein receptors on tissues such as liver and adrenocortical cells. Following the receptor mediated uptake by adrenocortical cells, NP-59 is etherified and stored in the intracellular lipid droplets but is not further metabolized [1, 22, 23]. NP-59 is well recognized to evaluate both hypersecreting and non-hypersecreting adrenal abnormalities. The main clinical questions for NP-59 scintigraphy in patients with hypercortisolism, hyperaldosteronism and hyperandrogenism are whether the disease is due to adenoma, or to bilateral hyperplasia or whether there is evidence of malignancy [7, 18, 19, 21, 64].

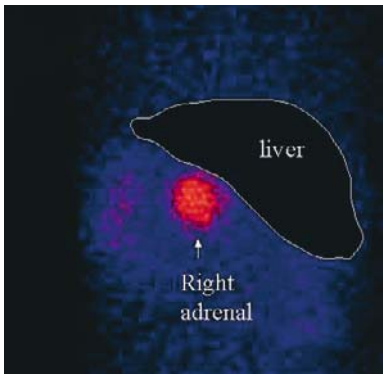


Fig. 9. ^{131}I-NP59 (norcholesterol) scintigraphy in a patient with primary aldosteronism demonstrating a focally increased tracer accumulation in right adrenal gland (dorsal view)

The imaging pattern of NP-59 scintigraphy can be compared with that of a thyroid scan, i.e. hormonally hypersecretory and non-hypersecretory adrenocortical adenomas demonstrate NP-59 accumulation and thus scintigraphic visualization on the side of the radiologically known adrenal mass. This is based on the fact that an adrenal adenoma is thought to represent non-malignant proliferation of adrenocortical cells able to accumulate greater amounts of NP-59. Non-functioning malignancies (primary or secondary) as well as other expansive lesions of the adrenal glands demonstrate decreased or an absent uptake by the affected gland [1, 7, 24, 56]. Bilaterally symmetrical NP-59 uptake is considered normal [14], while bilaterally increased uptake is consistent with bilateral hyperactive disease [22, 25, 53]. A number of studies have indicated that the degree of adrenocortical NP-59 uptake correlates with the level of hormonal hypersecretion [22, 24].

In patients with primary aldosteronism the overall sensitivity of combined NP-59 scan and CT was 100% [46]. Thus norcholesterol scintigraphy and CT seem necessary to confirm exclusive unilateral adrenal hyperfunction and, subsequently, establish the appropriate treatment [46].

Apart from NP-59, several other adrenocortical radiopharmaceuticals such as ^{131}I-19-iodocholesterol and ^{75}Se-selenomethyl-norcholesterol which have a similar uptake mechanism are used for adrenocortical imaging [25]. As shown recently [45], ^{75}Se-selenomethyl-norcholesterol represents the most sensitive and specific method of adrenal imaging study in patients with Cushing's syndrome compared to CT and MRI.

5.7.1.1 Patient Premedication

Thyroid Blockade ▶ Uptake of free ^{131}I derived from in vivo deiodination should be inhibited by oral adminis-

tration of saturated potassium iodide (100–200 mg/day, orally) starting 24 h prior to and throughout the imaging sequences and should be continued for about 1 week. Inadequate thyroid blockade leads to scintigraphic visualization of the thyroid gland and a substantial radiation exposure [7, 20, 24].

Laxatives ▶ To reduce potentially non-specific colonic radioactivity, 2 days before the 1st day of planned imaging, a mild laxative (10 mg bisacodyl) can be given [7, 22, 24, 70].

5.7.1.2 Interfering Drugs

Administration of drugs that might interfere with scintigraphic studies have to be interrupted before and during scintigraphy to avoid misinterpretation of the scintigraphic findings. This includes glucocorticoids, diuretics, spironolactone, beta- and calcium channel blockers, alpha-blockers and agents which interfere with the hypothalamic-pituitary adrenal axis and the renin-angiotensin–aldactone-system [7, 20, 22, 24, 53, 71].

In the case of aldosteronism, dexamethasone suppression is necessary to optimize the sensitivity of NP-59 scintigraphy. Dexamethasone suppresses the normal ACTH sensitive adrenal cortical function of corticoid production and has two important advantages: firstly, and most importantly, is the distinction between hyperplasia and adenoma, and, secondly, the reduction of radiation exposure to the normal adrenal gland. Dexamethasone is given at a dose of 0.5–1 mg 4 times a day starting 7 days prior to the tracer dose until the last day of the scintigraphy [7, 33, 64].

5.7.1.3 Scintigraphy

The usual dose of NP-59 is 1 mCi (37 MBq) administered by slow intravenous injection. Scintigraphic evaluation is possible 3–7 days after NP-59 application depending on the clinical situation. Planar images of a posterior view with a 256×256 matrix (high-energy collimator, 50,000–100,000 cts per image) are obtained on day 3 or 4 in patients with hyperaldosteronism and on day 5 after NP-59 administration in other clinical scenarios. If needed, additional images can be obtained on day 6 and 7 post NP-59 injection to give additional anatomical information. In some patients, additional acquisitions in a lateral projection may be required to assist in adrenocortical localization. Likewise, ^{99m}Tc-DTPA or ^{99m}Tc-DMSA scintigraphy of the kidneys may be necessary for a better anatomic identification of the tumor location, which can be done on the 5th or 7th day of the study. If ectopic adrenocortical tumor or tissue remnants are suspected, whole-body imaging has to be performed [7, 33, 64].

Although adrenocortical scintigraphy is able to provide an important contribution to identifying functional behavior of adrenal lesions, adrenocortical scanning is a laborious, time-consuming investigation and its results are dependent on the tumor size [81]. This method has a high overall sensitivity and specificity, although it is not able to give 100% true positive results [22, 33, 68, 83].

5.7.2 Adrenomedullary Imaging with ^{131}I- or ^{123}I-labeled Metaiodobenzylguandine

Chromaffin tumors can affect one or both adrenals (pheochromocytoma) or are localized outside the adrenal gland (paragangliomas). Paragangliomas can be found from the base of the skull to the pelvic diaphragm [59, 77]. They can appear as sporadic lesions or hereditary as part of the multiple endocrine neoplasia syndromes type 2A and 2B, Recklinghausen's neurofibromatosis, von-Hippel-Lindau disease or with the Sturge-Weber syndrome [59, 64, 76].

Most sporadic adrenomedullary tumors are benign, and are mostly localized in one adrenal [59]. Hereditary tumors are very often found in both adrenal glands.

Since appropriate therapy is highly dependent upon reliable exclusion of multifocality or metastatic disease, preoperative localization by scintigraphy is mandatory. For this reason and because of the introduction of minimal invasive surgery in recent years, accurate clinical staging of the disease is now of utmost importance. Of these nuclear medicine modalities, ^{123}I- or ^{131}I-labeled metaiodobenzylguanidine (MIBG) is a well-established radiopharmaceutical sensitive and specific for localization of phechromocytoma and paraganglioma since its initial clinical introduction in 1981 [5, 72].

MIBG is a functional and structural analog of the neurotransmitter norepinephrine that exploits the amine precursor uptake mechanism and is incorporated into vesicles or neurosecretory granules in the cytoplasm [31, 72, 74, 79, 80]. MIBG intensity in MIBG-avid tissue is a balance between uptake, storage capacity as well as tracer turnover. These properties of MIBG have led to the use of labeled MIBG to visualize chromaffin tumors (Fig. 10). This technique permits non-invasive and safe localization of pheochromocy-

Fig. 10. ^{123}I-MIBG scintigraphy in a patient with a pheochromocytoma in the left adrenal gland. *Left* dorsal view, *right* ventral view

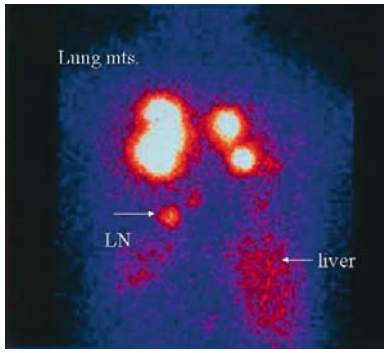


Fig. 11. ^{123}I-MIBG scintigraphy in a 77-year-old female patient with a malignant pheochromocytoma 17 years after primary surgery. Note the multiple MIBG-avid lesions in the thorax and abdomen (LNN metastases). Patient selected for ^{131}I-MIBG therapy

toma and paraganglioma with several advantages over anatomical radiological images. One significant advantage of MIBG scintigraphy over radiological imaging techniques is the possibility of whole body evaluation with a single administration of the radiotracer. Other advantages of MIBG scintigraphy are the low rate of false-positive, and when labeled with ^{123}I, the low rate of false-negative, results, and its high sensitivity and specificity in postoperative patients with distorted anatomy [59]. After intravenous injection, MIBG is distributed throughout the body. The normal MIBG biodistribution includes depiction of salivary glands, lacrimal glands, heart and spleen based on the extensive sympathetic innervation of these tissues. The distribution of radiolabeled MIBG within the limbs shows modest diffuse activity within the muscles and none within the long bones. Excretory organs such as the kidneys, urinary bladder, liver and intestine are also visualized. Of the radiolabeled MIBG, 55–60% is excreted through the kidneys in the first 24 h. The normal adrenal medulla may be seen with ^{123}I-labeled MIBG; it is, however, only rarely visualized with ^{131}I-labeled MIBG [54, 55, 72]. Any focal MIBG accumulation at sites not described above is strongly suspicious for MIBG-avid abnormal tissue.

The main clinical questions for MIBG scintigraphy in patients with adrenomedullary hypersecretion are whether the secreting tumor is localized in or outside the adrenal gland, whether the tumor site is uni- or bilateral or whether there is evidence of malignancy (Fig. 11).

5.7.2.1 Patient Premedication

Thyroid Blockade ▶ To avoid uptake of free iodine in the thyroid, there is a need for thyroid blockade because of the iodine content of the radiolabeled MIBG. Starting 2 days before administration of ^{131}I-MIBG, 100–200 mg saturated potassium iodine/day should be administered for 1 week. If ^{123}I-MIBG is administered for adrenomedullar scintigraphy, a thyroid blockade for only 2 days starting the day before MIBG injection can also be done with saturated potassium iodine (100–200 mg/orally, daily).

Laxatives ▶ For better evaluation of the abdomen, the intake of laxatives (e.g. bisacodyl 10 mg) 1 or better still 2 days before scintigraphy is recommended.

5.7.2.2 Interfering Drugs

It is known that MIBG uptake is hampered by a large number of drugs. Thus drugs known to interfere with MIBG uptake have to be interrupted to prevent drug interference. These drugs include tricyclic antidepressants (amitriptyline, imipramine), sympathomimetics (phenylephrine, phenylpropanolamine, pseudoephrine, ephedrine and cocaine), and antihypertensive/cardiovascular drugs (labetolol, reserpine and calcium channel blockers). Another group of drugs which in principle may also interfere with MIBG has not yet been confirmed clinically or experimentally [7, 32, 33, 72, 74].

5.7.2.3 ^{123}I-MIBG Scintigraphy

^{123}I has better physical characteristics and higher photon efficiency with consequently better image quality than ^{131}I-MIBG and thus is the radiopharmaceutical of choice. Due to the shorter physical half-life and lower number of particulate emissions, ^{123}I-MIBG has a more favorable radiation dosimetry, and approximately 20 times higher diagnostic doses can be administered when compared with ^{131}I-MIBG [7]. ^{123}I-MIBG per-

mits better localization and clearer delineation of small lesions and also allows SPECT (single photon emission computer tomography) imaging. ^{123}I-MIBG scintigraphy is performed 24 h after administration of 185–370 MBq ^{123}I-MIBG, which should be administered as a slow intravenous injection to avoid potential side effects such as hypertensive crises or tachycardia. If non-specific tracer accumulation is suspected in the kidneys and/or in the intestine, a delayed image may be necessary up to 72 hours postinjection. Although ^{123}I-MIBG is the radiopharmaceutical of choice, its use is limited because of the higher costs and due to the fact that ^{123}I-MIBG is not commercially available in all countries [7, 33, 64, 72]. ^{131}I-MIBG which is commercially available also gives very good results despite its suboptimal physical properties.

For better orientation whole-body acquisition (10 cm/min) in anterior and posterior views with a low-energy collimator is helpful. Thoracic and abdominal planar projections (anterior and posterior, matrix 256x256) are obligatory. For each acquisition 300–800 Kcts are needed. The additional SPECT technique of the abdomen and/or other suspected regions is important for recognition of small lesions and for better correlation with radiological techniques.

5.7.2.4 ^{131}I-MIBG

Clinical imaging is performed 1, 2, and 3 days after ^{131}I-MIBG administration of 17–37 MBq by intravenous injection. Gamma camera procedures have to be performed with planar views of the pelvis, abdomen, thorax and skull in anterior and posterior projections (matrix 265×265) with a high energy collimator. A quantity of 50–100 Kcts is needed for each planar acquisition. In some cases, lateral views of a region are important to define overlapping of organs. If the anatomical localization of the lesions depicted is not possible with ^{131}I-MIBG alone, simultaneous scintigraphies such as those of bone scan; renogram; or cardiac or liver scans may be helpful. Due to the long half-life of ^{131}I, scintigraphic evaluation is possible up to 5–7 days after injection of ^{131}I-MIBG, and this is occasionally useful [72].

5.7.3 Positron Emission Tomography

^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) has been proposed in nuclear oncology to evaluate tumor metabolism, especially providing functional information to characterize adrenal masses [65]. However, limited dates are available regarding the role of FDG and ^{11}C-metomidate PET in patients with adrenal masses [6, 49]. Further studies must be performed to define the role of PET in the diagnostic algorithm of adrenal lesions.

5.8 The Value of Imaging Studies for the Surgeon

The radiological work-up of diseases affecting the adrenal gland should start with appropriate biochemical screening tests followed by thin-collimation CT. If the results of CT are not diagnostic, MRI and in selected cases nuclear medicine imaging examinations should be performed.

The probability of an adrenal mass being malignant has been shown to increase significantly with its size (greatest diameter). But not all growing lesions are malignant [3, 4, 8, 48, 73]. A malignant-to-benign ratio of 8:1 has been reported in masses greater than 4 cm in diameter, thus prompting the recommendation for the systematic removal of a mass above that size and for enlarging lesions on follow-up examinations. Management strategies based on adrenal tumor size alone are neither sensitive nor specific, and tend to miss smaller and perhaps more surgically amenable lesions. Recommendations have been made that all lesions greater than 4 cm should be removed [45]. This approach would have the consequence that many more benign than malignant masses would be subjected to surgery, with attendant cost and risks. Many studies show that (multidetector) CT and dynamic gadolinium enhanced MRI with CSS are useful single investigations to predict the status of adrenal tumors in up to 95%. At least one of these investigations should be applied prior to planning the surgical strategy (minimally invasive adrenal versus open adrenal surgery) independent of the tumor size and function for planning surgery. Unforeseen conversion to open surgery and intraoperative complications (laceration of tumor capsule) can be reduced or prevented [28]. Tumor size alone is not suitable to predict the status of adrenal lesions. Taking into account tumor size and the results of preoperative imaging (CT or MRI), up to 70% of patients selected for surgery are suitable for endoscopic adrenalectomy [62]. Even tumors larger than 6 cm, classified as benign by CT or MRI, may be removed laparoscopically by endocrine surgeons experienced in endoscopic adrenalectomy [15, 29, 60].

In selected cases adrenocortical or adrenomedullary scintigraphic imaging of the adrenal glands is mandatory to localize the tumor within the gland, to exclude extra adrenal disease, multifocality or distant spread in a single procedure [17, 59, 63].

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